

Answer 1:

Bibliographic Information

17 α -estradiol inhibits LAPC-4 prostatic tumor cell proliferation in cell cultures and tumor growth in xenograft animals.

Qiao, Yaming; Zhang, Zhi-Kai; Cai, Li-Qun; Tan, Chen; Imperato-McGinley, Julianne L.; Zhu, Yuan-Shan. Department of Medicine/Endocrinology, Weill Medical College of Cornell University, New York, NY, USA. Prostate (Hoboken, NJ, United States) (2007), 67(16), 1719-1728. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 148:206766 AN 2008:54995 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Blockade of androgen activity is a major effective therapy for advanced prostate cancer. Estrogen analogs have been used for prostate cancer therapy for years presumably by inhibiting testosterone biosynthesis, but with considerable adverse events due to their classic estrogenic activity. With the discovery of the estrogen receptor (ER) β and its presence in prostate tumor cells, evaluation of estrogen analogs with less classic estrogenic activity in prostate cancer therapy is emerging. **Methods:** The effects of 17 α -estradiol (α E2), a stereo-isomer of 17 β -estradiol (β E2), on dihydrotestosterone (DHT)-induced cell growth and gene expressions were examd. in androgen-dependent LAPC-4 prostatic tumor cells and in LAPC-4 xenograft animals, and compared to those of β E2. **Results:** Both α E2 and β E2 attenuated DHT induction of PSA gene expression, cell proliferation, and cell growth in cultured LAPC-4 cells. The inhibition of cell proliferation was assocd. with a blockade of DHT-induced cyclin A and cyclin D1 expression by α E2 and β E2. In LAPC-4 xenograft mice, α E2 significantly inhibited tumor growth without altering the plasma testosterone level, while β E2 failed to inhibit tumor growth even though it significantly inhibited PSA gene expression. **Conclusion:** α E2 is an effective agent for inhibition of DHT-induced PSA, cyclin A, cyclin D1 gene expression, and cell proliferation in LAPC-4 cells, and tumor growth in LAPC-4 xenograft mice.

Answer 2:

Bibliographic Information

The combination of antagonists of LHRH with antagonists of GHRH improves inhibition of androgen sensitive MDA-PCa-2b and LuCaP-35 prostate cancers.

Stangelberger, Anton; Schally, Andrew V.; Zarandi, Marta; Heinrich, Elmar; Groot, Kate; Havt, Alexandre; Kanashiro, Celia A.; Varga, Jozsef L.; Halmos, Gabor. Veterans Affairs Medical Center, Tulane University School of Medicine, New Orleans, LA, USA. Prostate (Hoboken, NJ, United States) (2007), 67(12), 1339-1353. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 148:558 AN 2007:1153686 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND: Antagonists of growth hormone-releasing hormone (GHRH) could extend the duration of response of androgen sensitive prostate cancers to androgen deprivation. **METHODS:** We investigated the effect of new GHRH antagonists MZ-J-7-118 and MZ-J-7-138 and LH-releasing hormone (LHRH) antagonist Cetrorelix or castration on androgen sensitive MDA-PCa-2b and LuCaP-35 prostate cancer models xenografted into nude mice. Animals bearing androgen-independent LuCaP-35V prostatic cancer model were also treated with MZ-J-7-118. **RESULTS:** Receptors for LHRH and GHRH were present in MDA-PCA-2b, LuCaP-35, and LuCaP-35V tumors. GHRH antagonists increased the inhibitory effect of surgical castration and LHRH antagonists on androgen sensitive MDA-PCA-2b and LuCaP-35 tumors. The time to relapse of androgen-dependent LuCaP-35 tumors was extended by GHRH antagonists. Growth of androgen-independent LuCaP-35V xenografts was also significantly inhibited by MZ-J-7-118. In MDA-PCA-2b tumors treatment with MZ-J-7-118 caused a significant decrease of VEGF and Cetrorelix or its combination with MZ-J-7-118 reduced EGF. The Bmax of EGF receptors was significantly reduced by Cetrorelix, MZ-J-7-118 and their combination. **CONCLUSIONS:** Our findings suggest that the use of a combination of antagonists of GHRH and LHRH could improve the therapy for androgen sensitive prostate cancer. Antagonists of GHRH could be also considered for treatment of androgen-independent prostate cancers.

Answer 3:

Bibliographic Information**Androgen induces adaptation to oxidative stress in prostate cancer: implications for treatment with radiation therapy.**

Pinthus, Jehonathan H.; Bryskin, Inna; Trachtenberg, John; Lu, Jiang-Ping; Singh, Gurmit; Fridman, Eduard; Wilson, Brian C. The Prostate Cancer Center, University Health Network, Toronto, ON, Can. Neoplasia (Ann Arbor, MI, United States) (2007), 9(1), 68-80. Publisher: Neoplasia Press Inc., CODEN: NEOPFL ISSN: 1522-8002. <http://www.neoplasia.com/pdf/manuscript/neo06739.pdf> Journal; Online Computer File written in English. CAN 147:160909 AN 2007:194262 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Radiation therapy is a std. treatment for prostate cancer (PC). The postulated mechanism of action for radiation therapy is the generation of reactive oxygen species (ROS). Adjuvant androgen deprivation (AD) therapy has been shown to confer a survival advantage over radiation alone in high-risk localized PC. However, the mechanism of this interaction is unclear. We hypothesize that androgens modify the radioresponsiveness of PC through the regulation of cellular oxidative homeostasis. Using androgen receptor (AR)+ 22rv1 and AR- PC3 human PC cell lines, we demonstrated that testosterone increased basal reactive oxygen species (bROS) levels, resulting in dose-dependent activation of phospho-p38 and pAKT, and increased expression of clusterin, catalase, and manganese superoxide dismutase. Similar data were obtained in three human PC xenografts; WISH-PC14, WISH-PC23, and CWR22, growing in testosterone-supplemented or castrated SCID mice. These effects were reversible through AD or through incubation with a reducing agent. Moreover, testosterone increased the activity of catalase, superoxide dismutases, and glutathione reductase. Consequently, AD significantly facilitated the response of AR+ cells to oxidative stress challenge. Thus, testosterone induces a preset cellular adaptation to radiation through the generation of elevated bROS, which is modified by AD. These findings provide a rational for combined hormonal and radiation therapy for localized PC.

Answer 4:

Bibliographic Information

Germ cell development in equine testis tissue xenografted into mice. Rath, R.; Honaramooz, A.; Zeng, W.; Turner, R.; Dobrinski, I. Center for Animal Transgenesis and Germ Cell Research, School of Veterinary Medicine, University of Pennsylvania, Kennett Square, PA, USA. Reproduction (Bristol, United Kingdom) (2006), 131(6), 1091-1098. Publisher: Bioscientifica Ltd., CODEN: RCUKBS ISSN: 1470-1626. Journal written in English. CAN 145:307100 AN 2006:923285 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Grafting of testis tissue from immature animals to immunodeficient mice results in complete spermatogenesis, albeit with varying efficiency in different species. The objectives of this study were to investigate if grafting of horse testis tissue would result in spermatogenesis, and to assess the effect of exogenous gonadotropins on xenograft development. Small fragments of testis tissue from 7 colts (2 wk to 4 years of age) were grafted under the back skin of castrated male immunodeficient mice. For 2 donor animals, half of the mice were treated with gonadotropins. Xenografts were analyzed at 4 and 8 mo post-transplantation. Spermatogenic differentiation following grafting ranged from no differentiation to progression through meiosis with appearance of haploid cells. Administration of exogenous gonadotropins appeared to support post-meiotic differentiation. For more mature donor testis samples where spermatogenesis had progressed into or through meiosis, after grafting an initial loss of differentiated germ cells was obsd. followed by a resurgence of spermatogenesis. However, if haploid cells had been present prior to grafting, spermatogenesis did not progress beyond meiotic division. In all host mice with spermatogenic differentiation in grafts, increased wt. of the seminal vesicles compared to castrated mice showed that xenografts were releasing testosterone. These results indicate that horse spermatogenesis occurs in a mouse host albeit with low efficiency. In most cases, spermatogenesis arrested at meiosis. The underlying mechanisms of this spermatogenic arrest require further investigation.

Answer 5:

Bibliographic Information

Pharmacologic Basis for the Enhanced Efficacy of Dutasteride against Prostatic Cancers. Xu, Yi; Dalrymple, Susan L.; Becker, Robyn E.; Denmeade, Samuel R.; Isaacs, John T. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA. Clinical Cancer Research (2006), 12(13), 4072-4079. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:74712 AN 2006:642703 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Prostatic dihydrotestosterone (DHT) concn. is regulated by precursors from systemic circulation and prostatic enzymes of androgen metab., particularly 5 α -reductases (i.e., SRD5A1 and SRD5A2). Therefore, the levels of expression SRD5A1 and SRD5A2 and the antiprostatic cancer growth response to finasteride, a selective SRD5A2 inhibitor, vs. the dual SRD5A1 and SRD5A2 inhibitor, dutasteride, were compared. **Exptl. Design:** Real-time PCR and enzymic assays were used to det. the levels of SRD5A1 and SRD5A2 in normal vs. malignant rat and human prostatic tissues. Rats bearing the Dunning R-3327H rat prostate cancer and nude mice bearing LNCaP or PC-3 human prostate cancer xenografts were used as model systems. Tissue levels of testosterone and DHT were detd. using liq. chromatog.-mass spectrometry. **Results:** Prostate cancer cells express undetectable to low levels of SRD5A2 but elevated levels of SRD5A1 activity compared with nonmalignant prostatic tissue. Daily oral treatment of rats with the SRD5A2 selective inhibitor, finasteride, reduces prostate wt. and DHT content but did not inhibit R-3327H rat prostate cancer growth or DHT content in intact (i.e., noncastrated) male rats. In contrast, daily oral treatment with even a low 1 mg/kg/d dose of the dual SRD5A1 and SRD5A2 inhibitor, dutasteride, reduces both normal prostate and H tumor DHT content and wt. in intact rats while elevating tissue testosterone. Daily oral treatment with finasteride significantly ($P < 0.05$) inhibits growth of LNCaP human prostate cancer xenografts in intact male nude mice, but this inhibition is not as great as that by equimolar oral dosing with dutasteride. This anticancer efficacy is not equiv., however, to that produced by castration. Only combination of dutasteride and castration produces a greater tumor inhibition ($P < 0.05$) than castration monotherapy against androgen-responsive LNCaP cancers.

In contrast, no response was induced by dutasteride in nude mice bearing androgen-independent PC-3 human prostatic cancer xenografts. **Conclusions:** These results document that testosterone is not as potent as DHT but does stimulate prostate cancer growth, thus combining castration with dutasteride enhances therapeutic efficacy.

Answer 6:

Bibliographic Information

Activation of membrane androgen receptors potentiates the antiproliferative effects of paclitaxel on human prostate cancer cells. Kampa, Marilena; Kogia, Christina; Theodoropoulos, Panayiotis A.; Anezinis, Ploutarchos; Charalampopoulos, Ioannis; Papakonstanti, Evangelia A.; Stathopoulos, Efstathios N.; Hatzoglou, Anastassia; Stournaras, Christos; Gravanis, Achille; Castanas, Elias. Departments of Experimental Endocrinology and Biochemistry, Univ. Crete, Sch. Med., Heraklion, Greece. Molecular Cancer Therapeutics (2006), 5(5), 1342-1351. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 145:262650 AN 2006:501531 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Genomic signaling mechanisms require a relatively long time to get into action and represent the main way through which steroid hormones affect target cells. In addn., steroids may rapidly activate cellular functions by non-genomic signaling mechanisms involving membrane sites. Understanding in depth the mol. mechanisms of the non-genomic action represents an important frontier for developing new and more selective pharmacol. tools for endocrine therapies. In the present study, we report that membrane-impermeable testosterone-bovine serum albumin (BSA) acts synergistically with paclitaxel in modifying actin and tubulin cytoskeleton dynamics in LNCaP (androgen sensitive) and DU-145 (androgen insensitive) human prostate cancer cell lines. In addn., coincubation of either cell line with testosterone-BSA and paclitaxel induced inhibition of cell proliferation and apoptosis. Finally, in vivo expts. in LNCaP and DU-145 tumor xenografts in nude mice showed that both agents decrease tumor mass, whereas testosterone-BSA enhances the effect of paclitaxel. Our findings suggest that chronic activation of membrane androgen receptors in vitro and in vivo facilitates and sustains for a longer time the antitumoral action of cytoskeletal acting agents.

Answer 7:

Bibliographic Information

Enhancement of intermittent androgen ablation by "off-cycle" maintenance with finasteride in LNCaP prostate cancer xenograft model. Eggener, Scott E.; Stern, Jeff A.; Jain, Pankaj M.; Oram, Shane; Ai, Junkui; Cai, Xiaoyan; Roehl, Kim A.; Wang, Zhou. Department of Urology, Northwestern University, Chicago, IL, USA. Prostate (Hoboken, NJ, United States) (2006), 66(5), 495-502. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 145:203086 AN 2006:371367 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Intermittent androgen ablation (IAA) was developed with the intention of delaying progression of prostate cancer to androgen-independence and improving quality of life. Our previous studies suggest that relative to dihydrotestosterone (DHT), testosterone (T) is a weak inducer of proliferation and a more potent inducer of differentiation. We hypothesize that administration of finasteride (F), a type-II 5- α -reductase inhibitor that increases T and decreases DHT, during the IAA "off-cycle" would enhance the efficacy. Methods: After LNCaP tumor establishment, nude mice were castrated and randomized to continuous androgen ablation (CAA), continuous androgen ablation plus finasteride (CAA + F), intermittent androgen ablation (IAA), or intermittent androgen ablation plus finasteride (IAA + F). Results: After one cycle of therapy, mice treated with IAA + F had significantly less tumor growth than the other treatment groups ($P = 0.002$). Mice treated with IAA + F had the best survival ($P = 0.048$) and were 3-5 times more likely to be alive 70 days following treatment initiation. Conclusions: IAA with finasteride provides the most favorable tumor growth kinetics and survival compared to both CAA and std. IAA.

Answer 8:

Bibliographic Information

Androgen causes growth suppression and reversion of androgen-independent prostate cancer xenografts to an androgen-stimulated phenotype in athymic mice. Chuu, Chih-pin; Hiipakka, Richard A.; Fukuchi, Junichi; Kokontis, John M.; Liao, Shutsung. Ben May Institute for Cancer Research, Department of Biochemistry and Molecular Biology and Committee of Cancer Biology, University of Chicago, Chicago, IL, USA. Cancer Research (2005), 65(6), 2082-2084. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 142:310147 AN 2005:255377 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Most prostate cancer patients develop androgen-independent recurrent prostate tumors a few years after androgen ablation therapy. No therapy, however, has been shown to substantially extend survival in these patients. Previously, we reported that androgen suppresses the growth of androgen-independent LNCaP prostate tumor cells both in vitro and in vivo. In cell culture, androgen receptor (AR)-rich androgen-independent LNCaP 104-R1 cells adapt to growth suppression by androgen and then their growth is androgen stimulated. Because maintaining androgen dependency of prostate tumor cells should prolong the usefulness of androgen ablation therapy, we detd. if androgen-independent prostate tumors would revert to an androgen-stimulated phenotype in vivo upon androgen treatment. Growth of the LNCaP 104-R1 tumors was suppressed by androgen, but tumors then adapted to suppression by androgen and growth became androgen stimulated. Tumor AR and prostate-specific antigen mRNA and protein were initially high in 104-R1 tumors but decreased during adaptation. Subsequent removal of androgen decreased the serum prostate-specific antigen level further and stopped the growth of the adapted tumors. Because androgen caused growth suppression and then reversion of androgen-independent tumors to an androgen-stimulated phenotype and because the growth of androgen-stimulated tumors could be restrained by androgen ablation, these results suggest a novel therapy for AR-pos. androgen-independent prostate cancer.

Answer 9:

Bibliographic Information

Establishment of spermatogenesis in neonatal bovine testicular tissue following ectopic xenografting varies with donor age.

Oatley, Jon M.; Reeves, Jerry J.; McLean, Derek J. Department of Animals Sciences and Center of Reproductive Biology, Washington State University, Pullman, WA, USA. *Biology of Reproduction* (2005), 72(2), 358-364. Publisher: Society for the Study of Reproduction, CODEN: BIREBV ISSN: 0006-3363. Journal written in English. CAN 142:151115 AN 2005:91560 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Ectopic testicular xenografting can be used to investigate spermatogenesis and as an alternative means for generating transgenic spermatozoa in many species. Improving the efficiency of spermatogenesis in xenografted testicular tissue will aid in the application of this approach. The present study was conducted to evaluate age-related differences in the establishment of spermatogenesis in grafted testicular tissue from bulls between 2 and 16 wk of life. Testicular tissue was ectopically xenografted under the skin on the backs of castrated nude mice and subsequently evaluated for growth, testosterone prodn., and establishment of spermatogenesis 24 wk after grafting. The greatest wt. increases occurred in donor tissue from calves of the ages 2, 4, and 8 wk compared with the ages of 12 and 16 wk. Recipient mouse serum testosterone concn. was at normal physiol. levels 24 wk after grafting, and no significant differences were detected between recipients grafted with testicular tissue from bull calves of different ages. The development of germ cells to elongated spermatids were obsd. in seminiferous tubules of grafts from donor calves of the ages 4, 8, 12, and 16 wk but not obsd. in grafts from 2-wk donors, which contained round spermatids as the most advanced germ cell stage. Grafts from 8-wk donors contained a significantly higher (10-fold) av. percentage of seminiferous tubules with elongated spermatids than all other donor ages. These data demonstrate differences in the ability of testicular tissue from donor animals of different ages to establish spermatogenesis following ectopic testicular xenografting.

Answer 10:

Bibliographic Information

Nude Mice as a Model for Gonadotropin-Induced Adrenocortical Neoplasia. Bielinska, M.; Genova, E.; Boime, I.; Parviainen, H.; Kiiveri, S.; Rahman, N.; Leppaeluoto, J.; Heikinheimo, M.; Wilson, D. B. Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA. *Endocrine Research* (2004), 30(4), 913-917. Publisher: Taylor & Francis, Inc., CODEN: ENRSE8 ISSN: 0743-5800. Journal written in English. CAN 143:75614 AN 2005:18606 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Certain inbred mice (e.g., DBA/2J, CE) develop sex steroid producing adrenocortical tumors following gonadectomy. This adrenal response is thought to result from an unopposed increase in circulating gonadotropins and/or a decrease in factor(s) of gonadal origin. To differentiate between these two possibilities, we utilized the NU/J strain of nude mice, which are immunol. compromised and therefore permissive to xenografts. One group of female nude mice was gonadectomized, while another group of females received xenografts of CHO cells stably transfected with human chorionic gonadotropin (hCG). After 1-2 mo, subcapsular adrenocortical neoplasms contg. sex steroid-producing cells were obsd. in both groups. We conclude that high levels of circulating gonadotropins are sufficient to induce adrenocortical tumorigenesis, even in the presence of intact gonads.

Answer 11:

Bibliographic Information

Microarray analysis of prostate cancer progression to reduced androgen dependence: Studies in unique models contrasts early and late molecular events. Sirotnak, F. M.; She, Yuhong; Khokhar, Nushmia Z.; Hayes, Paula; Gerald, William; Scher, Howard I. Department of Medicine, Program of Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. *Molecular Carcinogenesis* (2004), 41(3), 150-163. Publisher: Wiley-Liss, Inc., CODEN: MOCAE8 ISSN: 0899-1987. Journal written in English. CAN 142:21130 AN 2004:984171 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Three unique variants of the CWR22 human prostate cancer xenograft model (CWR22LD1, LD2, and LD3) with a decrease in dependence on androgens were selected under non-castrate conditions, i.e., by outgrowth after transplantation into male NCR (AT) nu mice without testosterone supplementation. These variants were unable to grow in castrated male mice. For comparison, a second set of variants with even less dependence on androgens (castrate-resistant) were derived following outgrowth from CWR22 (CWR22Rv1 and RC) or CWR22LD1 (CWR22RS) after transplantation in castrated male mice. The androgen receptor (AR) gene in the CWR22LD variants was transcriptionally active and was neither mutated nor significantly overexpressed compared to CWR22. Oligonucleotide microarray anal. showed distinctly different profiles of dysregulated gene expression among the CWR22LD variants. Groups of only 26-41 genes were dysregulated greater than threefold with a different proportion of up vs. downregulated genes in each variant. Only one of the castrate-resistant variants (CWR22Rv1) had a highly overexpressed AR gene but AR in this variant and the two other castrate-resistant variants, CWR22 RS and RC, was not mutated beyond that seen in CWR22. In contrast to the CWR22LD variants, a total of 342, 295, and 222 genes were dysregulated at least threefold in CWR22Rv1, CWR22RS, and CWR22RC, resp., differing as well in the proportion of up vs. downregulated genes. Many of the genes dysregulated in CWR22LD1, LD2, and LD3 were further dysregulated in CWR22Rv1, RC, or RS. The most downregulated gene was microseminoprotein beta (MSPB). Along with cyclin D1, the most upregulated gene by an order of magnitude compared to other upregulated genes was hepatocyte growth factor (HGF) (scatter factor). These results suggest that the onset in the loss of androgen dependence in CWR22 proceeds through multiple pathways and does not require any direct change in the status of AR.

However, up-regulation of other survival pathways like that involving HGF in these studies could co-activate AR signaling. The endogenous overexpression of genes regulating sterol biosynthesis also obsd. in castrate-resistant CWR22 variants delineated a clin. relevant, compensatory mechanism for overcoming androgen deprivation re-affirming a central role for AR signaling in this process.

Answer 12:

Bibliographic Information

NE-10 Neuroendocrine Cancer Promotes the LNCaP Xenograft Growth in Castrated Mice. Jin, Ren Jie; Wang, Yongqing; Masumori, Naoya; Ishii, Kenichiro; Tsukamoto, Taiji; Shappell, Scott B.; Hayward, Simon W.; Kasper, Susan; Matusik, Robert J. Departments of Urologic Surgery, The Vanderbilt Prostate Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA. Cancer Research (2004), 64(15), 5489-5495. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 141:204582 AN 2004:619605 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Increases in neuroendocrine (NE) cells and their secretory products are closely correlated with tumor progression and androgen-independent prostate cancer. However, the mechanisms by which NE cells influence prostate cancer growth and progression, esp. after androgen ablation therapy, are poorly understood. To investigate the role of NE cells on prostate cancer growth, LNCaP xenograft tumors were implanted into nude mice. After the LNCaP tumors were established, the NE mouse prostate allograft (NE-10) was implanted on the opposite flank of these nude mice to test whether NE tumor-derived systemic factors can influence LNCaP growth. Mice bearing LNCaP tumors with or without NE allografts were castrated 2 wk after NE tumor inoculation, and changes in LNCaP tumor growth rate and gene expression were investigated. After castration, LNCaP tumor growth decreased in mice bearing LNCaP tumors alone, and this was accompanied by a loss of nuclear androgen receptor (AR) localization. In contrast, in castrated mice bearing both LNCaP and NE-10 tumors, LNCaP tumors continued to grow, had increased levels of nuclear AR, and secreted prostate-specific antigen. Therefore, in the absence of testicular androgens, NE secretions were sufficient to maintain LNCaP cell growth and androgen-regulated gene expression in vivo. Furthermore, in vitro expts. showed that NE secretions combined with low levels of androgens activated the AR, an effect that was blocked by the antiandrogen bicalutamide. Because an increase in AR level has been reported to be sufficient to account for hormone refractory prostate cancers, the NE cell population ability to increase AR level/activity can be another mechanism that allows prostate cancer to escape androgen ablation therapy.

Answer 13:

Bibliographic Information

Studies with CWR22 xenografts in nude mice suggest that ZD1839 may have a role in the treatment of both androgen-dependent and androgen-independent human prostate cancer. Sirotnak, Francis M.; She, Yohung; Lee, Fei; Chen, Jing; Scher, Howard I. Program in Molecular Pharmacology and Therapeutics and Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Clinical Cancer Research (2002), 8(12), 3870-3876. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 139:143462 AN 2002:974069 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

These studies examd. the effect of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor ZD1839 (Iressa) on CWR22 prostate tumors in nude mice. The effect of ZD1839 was also examd. in combination with either bicalutamide (Casodex) or cytotoxic agents against a hormone-dependent or -independent variant of CWR22, resp. The xenografts were grown for 4-7 days, then tumor measurements were made and therapy initiated. ZD1839 and bicalutamide were given p.o. on a once-daily, 5-day schedule for 2 successive weeks. Carboplatin and paclitaxel were given every 3-4 days for a total of four doses. Measurements of tumor vol. were made twice weekly during treatment and for 2 wk after treatment. The effect of ZD1839 on EGFR function was assessed by Western blotting of EGFR and its phosphorylated form in CWR22 and variant tumors before and after treatment with this agent. ZD1839 at its max. tolerated dose (150 mg/kg) inhibited the growth of androgen-dependent CWR22 by 54%, and the growth of two variants with different degrees of androgen independence and androgen receptor gene expression (CWR22LD1 and CWR22RV1) by 76%. The effects of ZD1839 were similar to those recorded for phosphorylation of EGFR as detd. by Western blotting. Co-administration of ZD1839 at its max. tolerated dose markedly increased the antiproliferative action of the antiandrogen bicalutamide against CWR22LD1. In fact, combining ZD1839 with a suboptimal dose of bicalutamide was more effective than a higher dose of bicalutamide alone. Co-administration of ZD1839, which required a 2-3-fold attenuation of dose to avoid toxicity, also markedly increased the therapeutic activity of carboplatin and paclitaxel against CWR22RV1, bringing about regression to a degree not seen with either agent alone. Tumor-free mice were seen only with the combination of ZD1839 and paclitaxel.

The results obtained in these related and highly relevant models of human prostate cancer suggest that ZD1839 may have a role in enhancing existing treatments of androgen-dependent and -independent forms of this disease in patients.

Answer 14:

Bibliographic Information

Regulation of FGF8 expression by the androgen receptor in human prostate cancer. Gnanapragasam, Vincent J.; Robson, Craig N.; Neal, David E.; Leung, Hing Y. School of Surgical Sciences, Prostate Research Group, University of Newcastle-upon-Tyne, Newcastle-upon-Tyne, UK. Oncogene (2002), 21(33), 5069-5080. Publisher: Nature Publishing Group, CODEN: ONCNES ISSN: 0950-9232. Journal written in English. CAN 137:308371 AN 2002:551822 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Fibroblast growth factor 8 (FGF8) has been shown to play a key role in prostate carcinogenesis. It was initially cloned as an androgen induced protein in mouse mammary cancer SC3 cells. In this study, we examd. if FGF8 was also regulated by the androgen receptor in human prostate cancer. FGF8b protein expression in resected clin. prostate cancer correlated closely with expression of the androgen receptor (AR). In the androgen sensitive CWR22 prostate xenograft, we obsd. up-regulation of FGF8b immunoreactivity in testosterone supplemented mice while castration markedly reduced its signal. Furthermore, FGF8b protein expression in AR pos. LNCaP cells was similarly enhanced by androgens. The proximal promoter of the human FGF8 gene was cloned into a luciferase reporter construct (FGF8.luc). FGF8.luc activity in AR pos. LNCaP and SC3 cells was increased 2.5-fold by androgens. In AR neg. DU145 cells, maximal induction of FGF8.luc required both co-transfection of the AR and the presence of androgens. The anti-androgen bicalutamide completely abolished AR mediated FGF8.luc induction. Deletion constructs from FGF8.luc have further defined an active promoter region and an androgen responsive region. Nucleotide anal. of this androgen responsive region has revealed putative androgen response elements. Finally, using ChIP assays we confirmed in vivo interaction between the AR and the androgen responsive region of the FGF8 promoter. Taken together these data provide first evidence that expression of the mitogen

FGF8 in prostate cancer is, at least in part, regulated by the androgen receptor at the transcriptional level.

Answer 15:

Bibliographic Information

Establishment and characterization of a human adrenocortical carcinoma xenograft model. Logie, Armelle; Boudou, Philippe; Boccon-Gibod, Liliane; Baudin, Eric; Vassal, Gilles; Schlumberger, Martin; Le Bouc, Yves; Gicquel, Christine. Laboratoire d'Explorations Fonctionnelles Endocriniennes, INSERM U-515, Hopital d'Enfants Armand Trousseau, Paris, Fr. Endocrinology (2000), 141(9), 3165-3171. Publisher: Endocrine Society, CODEN: ENDOAO ISSN: 0013-7227. Journal written in English. CAN 133:294433 AN 2000:603823 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Adrenocortical carcinomas are rare malignant tumors. They have a poor prognosis, as they are often diagnosed late and are usually resistant to chemotherapy. The lack of a suitable animal model for these tumors has been a major obstacle to the evaluation of new therapeutic agents. The aim of this study was to establish and characterize xenografts of the human adrenocortical carcinoma NCI H295R cell line as a model of adrenocortical carcinoma for future therapeutic trials. This cell line was s.c. injected (6×10^6 cells) into nude mice ($n = 20$). Solid tumors were locally measurable after 45 days at 90% of the inoculation sites. The xenografts were similar histol. to the original adrenocortical carcinoma from which the cell line was derived. The xenografts precisely reproduced the dysregulation of the insulin-like growth factor (IGF) system [overexpression of the IGF-II and IGF-binding protein-2 (IGFBP-2) genes] typical of adrenocortical carcinoma. Similarly to adrenocortical carcinomas, human IGFBP-2 (but not IGF-II) was secreted in mouse plasma. 17-Hydroxyprogesterone We analyzed steroid prodn. (cortisol, 17-hydroxypregnenolone, 17-hydroxyprogesterone, dehydroepiandrosterone, $\Delta 4$ -androstenedione, 11-deoxycortisol, corticosterone, and testosterone). Xenografts produced all three class of steroids, with the preferential prodn. of androgens of the $\Delta 4$ pathway. The H295R xenograft model is a good model of human adrenocortical carcinoma, as it mimics dysregulation of the IGF system usually found in these tumors. It also produces IGFBP-2 and steroids that can be used as tumor markers. This model may therefore be useful for evaluating therapeutic agents.

Answer 16:

Bibliographic Information

Intermittent androgen suppression in the LuCaP 23.12 prostate cancer xenograft model. Buhler, Kent R.; Santucci, Richard A.; Royai, Ramin A.; Whitney, Sarah C.; Vessella, Robert L.; Lange, Paul H.; Ellis, William J. Department of Urology, University of Washington, Seattle, WA, USA. Prostate (New York) (2000), 43(1), 63-70. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 133:145091 AN 2000:253906 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND. Intermittent androgen suppression (IAS) has been proposed as a method of delaying the onset of androgen-independent growth in prostate cancer. While several pilot studies have demonstrated the feasibility of such a treatment, no study to date has defined the effect of IAS on survival. **METHODS.** We developed an IAS protocol for mice bearing the LuCaP 23.12 human prostate cancer xenograft, with each cycle consisting of 1 wk of androgen replacement with a testosterone pellet followed by 3 wk of androgen withdrawal. Mice that responded to castration with a 40% or greater decrease in serum prostate-specific antigen (PSA) were randomized to treatment with either continuous androgen suppression (CAS) or IAS. Serum PSA, tumor vol., and overall survival were monitored. **RESULTS.** A total of 75 mice met the randomization criteria. There was no significant difference of survival between animals treated with CAS or IAS (185 vs. 239 days, $P = 0.1835$). Serum PSA showed evidence of cycling with hormonal manipulation. No cycling was noted in tumor vol. **CONCLUSIONS.** IAS is not assocd. with a decrease in survival compared to CAS, yet in patients may offer quality-of-life improvements. Further studies of IAS in the setting of Institutional Review Board (IRB) approved clin. trials should be encouraged.

Answer 17:

Bibliographic Information

Switch from antagonist to agonist of the androgen receptor blocker bicalutamide is associated with prostate tumour progression in a new model system. Culig, Z.; Hoffmann, J.; Erdel, M.; Eder, I. E.; Hobisch, A.; Hittmair, A.; Bartsch, G.; Utermann, G.; Schneider, M. R.; Parczyk, K.; Klocker, H. Department of Urology, University of Innsbruck, Innsbruck, Austria. *British Journal of Cancer* (1999), 81(2), 242-251. Publisher: Churchill Livingstone, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 132:131907 AN 1999:658147 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Advanced prostate cancer is treated by androgen ablation and/or androgen receptor (AR) antagonists. To investigate the mechanisms relevant to the development of therapy-resistant tumors, the authors established a new tumor model which closely resembles the situation in patients who receive androgen ablation therapy. Androgen-sensitive LNCaP cells were kept in androgen-depleted medium for 87 passages. The new LNCaP cell subline established in this manner, LNCaP-abl, displayed a hypersensitive biphasic proliferative response to androgen until passage 75. Maximal proliferation of LNCaP-abl cells was achieved at 0.001 nM of the synthetic androgen methyltrienolone (R1881), whereas 0.01 nM of this compd. induced the same effect in parental cells. At later passages (> 75), androgen exerted an inhibitory effect on growth of LNCaP-abl cells. The non-steroidal anti-androgen bicalutamide stimulated proliferation of LNCaP-abl cells. AR protein expression in LNCaP-abl cells increased approx. fourfold. The basal AR transcriptional activity was 30-fold higher in LNCaP-abl than in LNCaP cells. R1881 stimulated reporter gene activity in LNCaP-abl cells even at 0.01 nM, whereas 0.1 nM of R1881 was needed for induction of the same level of reporter gene activity in LNCaP cells. Bicalutamide that acts as a pure antagonist in parental LNCaP cells showed agonistic effects on AR transactivation activity in LNCaP-abl cells and was not able to block the effects of androgen in these cells. The non-steroidal AR blocker hydroxyflutamide exerted stimulatory effects on AR activity in both LNCaP and LNCaP-abl cells; however, the induction of reporter gene activity by hydroxyflutamide was 2.4- to 4-fold higher in the LNCaP-abl subline. The changes in AR activity were assocd. neither with a new alteration in AR cDNA sequence nor with amplification of the AR gene. Growth of LNCaP-abl xenografts in nude mice was stimulated by bicalutamide and repressed by testosterone.

In conclusion, the results show for the first time that the non-steroidal anti-androgen bicalutamide acquires agonistic properties during long-term androgen ablation. These findings may have repercussions on the natural course of prostate cancer with androgen deprivation and on strategies of therapeutic intervention.

Answer 18:

Bibliographic Information

Immunohistochemical quantitation of androgen receptor expression using color video image analysis. Kim, Desok; Gregory, Christopher W.; Smith, Gary J.; Mohler, James L. Department of Surgery, Division of Urology, The Laboratories for, University of North Carolina, Chapel Hill, NC, USA. *Cytometry* (1999), 35(1), 2-10. Publisher: Wiley-Liss, Inc., CODEN: CYTODQ ISSN: 0196-4763. Journal written in English. CAN 130:276905 AN 1999:64341 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: The immunostaining features of the androgen receptor (AR) have been studied in prostate cancer (CaP) to predict the outcome of androgen deprivation therapies. We have developed an automatic video color image anal. system for quantitation of AR expression in large samples of prostatic nuclei. **Methods:** Essential criteria of immunostaining have been examd. to establish a linear relationship between AR protein content and mean optical d. (MOD) of the immunoperoxidase-substrate reaction product. Titrn. of monoclonal AR antibody, F39.4.1, and concn. and reaction time of substrate were optimized using color video image anal. The methodol. was tested twice. First, CWR22 human CaP xenograft specimens, harvested from testosterone (T)-stimulated, castrated and T-resupplemented mice, were immunostained to demonstrate the dependence of AR expression on serum androgen levels. Second, AR expression was measured in archived clin. specimens. **Results:** In CWR22 tumor-bearing mice castrated for 6 days, AR

MOD decreased to 57% of T-stimulated, intact mice. After 72 h of T treatment, AR MOD returned to the level measured in T-stimulated, intact mice. Sixteen radical prostatectomy specimens and 16 transurethral resection of prostate (TURP) specimens were double-labeled with F39.4.1 and anti-cytokeratin MAb (13 β E12) specific for basal epithelial cells. Benign epithelial cells exhibited lower AR MOD in prostatectomy compared to TURP specimens. Differences in AR immunostaining intensity may have resulted from differences in tissue fixation of whole organ vs. small tissue specimens. Conclusions: AR immunostaining can be quantitated accurately using optimized immunohistochem. criteria and video image anal.

Answer 19:

Bibliographic Information

Human primary prostate tumor cell line, ALVA-31: A new model for studying the hormonal regulation of prostate tumor cell growth. Loop, Stephen M.; Rozanski, Thomas A.; Ostenson, Richard C. Res. Serv., Dep. Veterans Aff. Med. Cent., Tacoma, WA, USA. Prostate (New York, NY, United States) (1992), 22(2), 93-108. CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 119:46475 AN 1993:446475 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A new human prostate tumor cell line (ALVA-31) has been established from a biopsy specimen of primary tumor obtained during prostatectomy. The cell line has been maintained for more than 48 mo in stable growth. The in vitro doubling time was detd. to be approx. 26 h. The chromosome no. ranged from 24-112, with a modal no. of 59 tested over several time points throughout continuous culture. Karyotypic anal. of late-passaged cells demonstrated approx. 70 human chromosomes, 8-14 markers, and two X chromosomes without a Y chromosome. Prostatic origin was confirmed by the expression of both prostate specific antigen and prostatic acid phosphatase, using specific antisera and immunoradiolabelling techniques. Prostate tumor xenografts were grown in intact male, castrated male, and female athymic mice; however, the rate of tumor growth was clearly dependent upon serum testosterone levels.

Answer 20:

Bibliographic Information

Hormonal influence on the growth of heterologously transplanted Ehrlich mouse ascites cancer. III. Effect of testosterone on the growth of cancer in hamster. Ahlstrom, C. G.; Stormby, N. Univ. Lund, Swed. Acta Pathologica et Microbiologica Scandinavica (1958), 43 34-40. CODEN: APMIAL ISSN: 0365-5555. Journal language unavailable. CAN 52:78426 AN 1958:78426 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Testosterone inhibits the growth of Ehrlich's mouse ascites cancer transferred to castrated male hamsters, but does not influence such growth in castrated females. The reason for this is not known.

Answer 21:

Bibliographic Information

Evidence of pluripotent human prostate stem cells in a human prostate primary xenograft model. Huss Wendy J; Gray Danny R; Werdin Eric S; Funkhouser William K Jr; Smith Gary J Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, North Carolina 27599, USA The Prostate (2004), 60(2), 77-90. Journal code: 8101368. ISSN:0270-4137. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 15162374 AN 2004263585 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

INTRODUCTION: The phenotypic plasticity of the human prostate stem cell within human prostate tissue was examined to determine the response of the stem cell to changes in the androgenic environment. **METHODS:** Prostate xenografts were transplanted into athymic nu/nu mice implanted with testosterone pellets, allowed to establish for 1 month time point, the hosts were castrated and pellets removed, and following 1 month of androgen deprivation, the hosts were stimulated with androgen for 2 days to induce proliferation of the residual population of stem cells (2-month time point). **RESULTS:** Glands in benign xenografts harvested at the 1- and 2-month time points contained basal cell layers that expressed p63 and high molecular weight cytokeratin, and in which essentially all of the cellular proliferation was localized, consistent with the proposed localization of the prostate stem cell. Benign glandular structures in the xenografts were populated by basal, secretory epithelial, neuroendocrine (NE), or squamous cells overlaying the basal cell layer, whereas, adenocarcinoma glands in the xenografts resembled the original prostate cancer (CaP) tissue. **CONCLUSIONS:** In this human prostate primary xenograft model, the residual stem cell population that survives transplantation, or androgen deprivation, maintains significant pluripotentiality as demonstrated by the capacity to generate progeny that differentiate along multiple lineages in response to microenvironmental signals, particularly along the secretory epithelial lineage in response to androgen, and along the NE cell lineage in response to androgen deprivation. Copyright 2004 Wiley-Liss, Inc.

Answer 22:

Bibliographic Information

Human primary prostate tumor cell line, ALVA-31: a new model for studying the hormonal regulation of prostate tumor cell growth. Loop S M; Rozanski T A; Ostenson R C Department of Veterans Affairs Medical Center, Tacoma, WA 98493 The Prostate (1993), 22(2), 93-108. Journal code: 8101368. ISSN:0270-4137. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.) written in English. PubMed ID 7681207 AN 93205622 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A new human prostate tumor cell line (ALVA-31) has been established from a biopsy specimen of primary tumor obtained during prostatectomy. The cell line has been maintained for more than 48 months in stable growth. The in vitro doubling time was determined to be approximately 26 hr. The chromosome number ranged from 24-112, with a modal number of 59 tested over several time points throughout continuous culture. Karyotypic analysis of late-passaged cells demonstrated approximately 70 human chromosomes, 8-14 markers, and two X chromosomes without a Y chromosome. Prostatic origin was confirmed by the expression of both prostate specific antigen and prostatic acid phosphatase, using specific antisera and immunoradiolabelling techniques. Prostate tumor xenografts were grown in intact male, castrate male, and female athymic mice; however, the rate of tumor growth was clearly dependent upon serum testosterone levels.

Answer 23:

Bibliographic Information

Androgen receptor in human normal and malignant pancreatic tissue and cell lines. Corbishley T P; Iqbal M J; Wilkinson M L; Williams R Cancer (1986), 57(10), 1992-5. Journal code: 0374236. ISSN:0008-543X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3955505 AN 86161352 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Estrogen and progestogen receptors have been demonstrated in human pancreatic adenocarcinoma tissue. Tumor growth

as xenografts in nude mice is promoted by testosterone and retarded by cyproterone acetate but is not influenced by estrogens, progestogens, or their antagonists, although estrogen receptors were demonstrated in xenograft cytosol. A new sensitive microassay technique for sex steroid receptors which relies on affinity chromatography was used in this study. With this assay, androgen receptors were detected in five fresh human pancreatic adenocarcinoma specimens (three male), two pancreatic cancer cell lines (Mia PaCa 2 and Ger), one xenograft tumor which responded to androgens, five specimens of normal adult pancreas (two male), and a pool of fetal pancreatic tissue. The similarity of the androgen receptor in pancreatic carcinoma to that of classical androgen target organs was demonstrated by sedimentation behavior and competitive binding studies. The improved sensitivity of the microassay allowed low levels of estrogen, androgen, and progesterone receptors to be detected in normal adult pancreatic tissue.

Answer 24:

Bibliographic Information

Immunobiology and therapeutic manipulation of heterotransplanted Nb rat prostatic adenocarcinoma. Chemotherapy of autonomous tumor, 102 Pr, heterotransplanted into congenitally athymic (nude) mice and syngeneic Nb rats. Drago J R; Maurer R E; Goldman L B; Gershwin M E Cancer chemotherapy and pharmacology (1979), 3(3), 167-70. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 118827 AN 80111501 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Nb rat prostatic adenocarcinomas, previously induced by the administration of testosterone and estrogen, have been serially studied as heterotransplants into congenitally athymic (nude) mice and into groups of Nb rats. This animal system has been used to evaluate the chemotherapeutic efficacy of 5-fluorouracil and Ftorafur. The use of both species was to determine if there would be any significant difference in relative tumor growth in nude mice which lack functional T cells as opposed to intact Nb rats. The autonomous tumor, 102 Pr, is the subject of the thesis presented herein. One donor Nb rat bearing 102 Pr prostatic adenocarcinoma served as the donor for this experiment. The nude mice and Nb rats received the transplant on the same date and were subjected to the chemotherapies outlined above and were treated after there was sufficient increase in tumor volume from the 2 mm³ wedge to assure growth and neovascularity (greater than 60 mm³). Statistically significant data was presented revealing 5-fluorouracil to be efficacious in the treatment of these tumors. Also presented is data revealing differences in growth versus time in the respective recipient animal hosts. It is suggested herein that this combination animal model system could be used for screening potential cytotoxic chemotherapeutic agents.